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Brief review

Biosimilars – terms of use

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Abstract

The impending expiry of the patent on a number of leading biologic drugs has led to a surge in the development of 'biosimilar' or 'follow-on' products. However, in contrast to generic small-molecule medicines, biosimilars are not identical to their reference products. The differences and complexities surrounding both the molecular structure and the manufacturing process for biologics and biosimilars have resulted in a lack of clarity regarding the terms used in different parts of the world to define various aspects of development and utilization such as regulatory approval, pharmacovigilance, interchangeability and treatment-naivety. This makes quantitative evaluation of biosimilars a great challenge to both the scientific community and regulatory agencies.

This manuscript attempts to clarify the terms used and address an important knowledge gap which is currently resulting in an increasing rush to position biosimilars for certain indications and patients in the absence of agreed upon definitions.

Introduction

The impending expiry of the patent on a number of leading biologics has led to a recent surge in the development of 'biosimilar' or 'follow-on' products[1]. However, in contrast to generic small-molecule medicines, biosimilars are not 'identical' to their reference product[1]. The complexity and heterogeneity of the molecular structure and the complicated manufacturing process make informed evaluation of biosimilars a great challenge to both the scientific community and regulatory agencies[2].

Use of biosimilar products has the potential to decrease the cost of treatment in many regions of the world, in turn making it accessible to many more patients. It is expected that the use of biosimilars will reduce pharmaceutical costs by 20–30% on average. With several top-selling biologics likely to lose patent exclusivity by 2020, bodies such as health insurers, regulatory agencies, reimbursement organizations and pharmaceutical and biotech companies are preparing for the availability of new biosimilars by addressing formulary management and therapeutic interchange issues, pharmacovigilance and patient safety concerns, and related financial and operational issues[3].

A regulatory pathway for approval of these products has now been firmly established in Europe with over 20 biosimilars (of six originator biologics) being approved since 2006. In the meantime many other countries have established the appropriate regulatory pathways for biosimilars, currently resulting in the approval of eight biosimilars in Australia, three in Canada, seven in Japan, three in Korea and one in the US. Despite this many clinicians are reluctant to consider biosimilars as a treatment option for their patients. Major concerns voiced about biosimilars relate to their pharmaceutical quality, safety (especially immunogenicity) and efficacy (particularly in extrapolated indications)[4].

Lack of awareness and information regarding these agents is a significant problem[5]. A study conducted in 2011 of 277 healthcare professionals (HCPs) indicated that 26%, 21% and 31% of pharmacists, physicians and nurses respectively, needed more information before making a decision about using biosimilars[6]. Respondents stated that evaluations which compared the chemical, physical and pharmacokinetic similarities of biosimilars and their reference products, plus safety and efficacy data were among the most important types of information they needed. In a separate survey, more than 57% of hospital pharmacists stated that confirmatory clinical trials comparing biosimilars to the branded originator biologic in each indication for which approval is sought, were necessary to prove biosimilarity[7].

Currently, it is generally accepted that biosimilars are most appropriately initiated in treatment-naïve patients, although definition of this is open to interpretation as no clear guidelines exist on this.

This manuscript attempts to address an important knowledge gap which is currently resulting in an increasing rush to position biosimilars for treatment-naïve patients in the absence of agreed upon definitions of naïvety per molecule and per indication.

Regulatory approval of biosimilars

The European Medicines Agency (EMA) was the first to establish the regulatory and scientific concepts for biosimilars[8]. Since then, implementation of the regulations has evolved with many other countries establishing their own national guidelines, but the definitions and terminology for biosimilarity vary[9,10].

The approval process for a biosimilar may be abridged with respect to the non-clinical and clinical requirements on the conditions that its physicochemical and in vitro functional properties have been shown to be highly similar to an already approved reference product[10]. However, this means that the amount of available clinical efficacy and safety data for the biosimilar will be less than that for an original product[11]. To cover this gap in the abbreviated approval pathway, and also to clarify any uncertainty regarding extrapolated indications, it is obligatory for biosimilar manufacturers to submit comprehensive pharmacovigilance plans when applying for approval[8].

Pharmacovigilance and traceability

An important concern with all biologic medicines is the potential for an unwanted immune response, thus the ability to track and trace such events is critical[12,13]. The WHO program for international drug monitoring is based on the principle of international collaboration in the field of pharmacovigilance. Over 100 member nations have systems in place that encourage HCPs to record and report adverse drug reactions[14].

Recently, new European pharmacovigilance legislation has been implemented which focuses on those medicines (both innovator biologics and biosimilars) that require additional monitoring, ensuring proper risk management through the recording of suspected adverse drug reactions and data collection from all stakeholders[15]. The new regulation entails a reduction of the administrative burden on companies and regulatory agencies, as obligations are clearly established and duplication of effort avoided[16]. These new guidelines impose the recording of the brand name and batch number. For biosimilars a 'black triangle' must be included in the product information to indicate that it is subject to additional monitoring as with new biologicals. A list of the EU-approved biosimilars currently requiring additional monitoring is shown in Table 1[16].

Pharmacovigilance of biologics and biosimilars should include processes that are easily used by prescribing practitioners to ensure that data are consistent and new safety signals are properly reported and assigned to the correct product[17]. Such surveillance can be accomplished by many means, including implementing patient registries and/or prospective or retrospective observational and epidemiological studies[18]. However, as with any patient registry data, the information is only as accurate as it is entered into a registry and could be misleading. Furthermore, the question remains as to how registries for the same indication from different countries can be pooled and analyzed to enable sufficient data for complete evaluation.

However post-marketing surveillance is conducted, it would be helpful for the international non-proprietary name (INN) to be recognized all over the world. Because generic chemical drugs are automatically assigned the same non-propriety name as the branded agent recognition is very straightforward, but the naming process for biosimilars is likely to be less so. Even though discussions are still ongoing as to whether the INN of a biosimilar should be distinct from that of the original biological, current practice in the EU is that the INN of a new biosimilar may be the same as that of the original biologic. Using the INN for prescription purposes will inevitably lead to situations in which the prescribing physician will not know to which medicine any adverse event data refers to. This may lead to the erroneous interpretation of a class effect when in fact the reference product (or indeed a biosimilar) may not be responsible. It is therefore strongly encouraged to prescribe biologicals in general and biosimilars in particular by brand name rather than INN[19] and the medical records should be accurate as to what product the patients receive.

This naming issue has recently prompted the World Health Organization to propose a new system of 'biological qualifiers' (BQs) to ensure that biosimilars can be more

Table 1. List of EU-approved biosimilars currently requiring additional monitoring*,[16].

Name	Active substance	Therapeutic area	Date of authorization
Accofil	filgrastim	Neutropenia	18/09/2014
Abasaglar (previously Abasria)	insulin glargine	Diabetes mellitus	09/09/2014
Bemfola	follitropin alfa	Anovulation	27/03/2014
Grastofil	filgrastim	Neutropenia	18/10/2013
Ovaleap	follitropin alfa	Anovulation	27/09/2013
Inflectra	infliximab	Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis Crohn's disease Psoriasis Ankylosing spondylitis	10/09/2013
Remsima	infliximab	Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis Crohn disease Psoriasis Ankylosing spondylitis	10/09/2013

*Biosimilars authorized after 1 January 2011. Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and summary of product characteristics, together with a short sentence explaining what the triangle means.

easily distinguished from their biologic counterparts. The BQ proposal suggests adding a unique four-letter code to complement the INN of a biological substance manufactured at a specific site with the aim of more easily identifying both the manufacturer and potentially the manufacturing site of the active substance[20]. It is questionable however as to what added value the addition of a BQ to the INN will provide to the traceability of a drug product, compared to the use of the brand name and batch number.

Interchangeability

Approval of a biosimilar does not mean that the medication is interchangeable with its reference product[21]. Because the regulatory pathway for biosimilars is abbreviated the available clinical efficacy and safety data are more limited than for their reference products[21].

According to the FDA a biosimilar product is a biological product that is approved based on it showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and efficacy from the reference product. An interchangeable biological product is biosimilar to an FDA-approved reference product and meets additional standards for interchangeability that include the same expected result in any given patient and no increased risks or decreased efficacy with multiple switches. Such an interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the healthcare provider who prescribed the reference product[22].

In Europe substitution policies are decisions outside the remit of the EMA because the regulation of substitution of medicinal products is the responsibility of the individual EU member states[4]. Long-term clinical investigations and systematic monitoring of the efficacy and tolerability of biosimilars in all indications are still needed[23], and even then establishing the interchangeability of biosimilar and innovator drugs will be difficult. Although it hasn't happened so far, it is possible in the future that some biosimilars might not carry the same indications as those for which the reference drug is approved[3].

Furthermore, individual countries outside the EU may exercise their own discretion with regard to the approval of biosimilars (and indeed other original medicinal products) for all the indications assigned to the originator drug. For example, two brands of the monoclonal antibody infliximab (IFX) from the Korean company Celltrion were approved as 'subsequent entry biologics' in Canada in January 2014 for some (but not all) approved indications for the existing brands. Inflectra/Remsima received two psoriasis indications (psoriasis and psoriatic arthritis) from extrapolation of the clinical data beyond the foundation indications for rheumatoid arthritis (RA) and ankylosing spondylitis. These 'extrapolated' approvals, however, did not extend to Crohn's disease and ulcerative colitis because the mode of action in this therapeutic area is potentially different from the mode of action in RA and ankylosing spondylitis[24].

The distinction between a designation of 'biosimilar' and 'interchangeable' is important, particularly when it comes to formulary decisions[25]. This situation is further complicated by the fact that a declaration of biosimilarity emphatically does not imply that a patient could be

switched from one product to another[26]. Switching means transitioning between the reference product and the biosimilar (or vice versa). Interchangeability refers to switching back and forth between the reference product and the biosimilar, and substitution is interchanged without the knowledge of the prescribing physician.

The FDA states that interchangeability should be proven by a clinical trial that shows no loss of efficacy and no increase in adverse events with repeated switching between the biosimilar and the reference compound[22]. However, the design of a clinical trial to prove this might be controversial. The experimental group would have to be switched repeatedly between the reference product and the biosimilar, whereas the control group would be treated with the reference product or the biosimilar alone. Without any prior understanding of the consequences from previous studies the experimental group might be at risk of loss of efficacy and/or increased safety concerns.

The Norwegian Medicines Agency is proactively encouraging a substitution culture and have initiated a clinical study to investigate the safety and efficacy of switching between IFX (Remicade) and the biosimilar Remsima in patients with RA, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis (ClinicalTrials.gov identifier: NCT02148640)[27]. The primary endpoint of the NOR-SWITCH study is the occurrence of disease worsening in the indications being studied[27]. However these endpoints cannot actually be analyzed (pooled) together and the sample size in each disease is underpowered to show a difference if it exists.

In France, a new law (beginning on 1 January 2014 but as yet to be implemented by decree) states that pharmacists will be legally permitted to substitute a biosimilar for the prescribed reference biological medicine as long as the prescribing physician has not marked the prescription as 'non-substitutable'[28]. Importantly, substitution will be allowed only when initiating a course of treatment, and if the biosimilar belongs to the same group as the prescribed product, known as a 'similar biologic group'. If the pharmacist decides to substitute a biosimilar for the prescribed biologic, he/she must both write the brand name of the dispensed product on the prescription and inform the prescribing physician in order to maintain an accurate medical record. These laws remain to be further defined in decrees from the Administrative Supreme Court, and thus biosimilar substitution should only occur in French practice after these decrees have been adopted[28].

Confusion around switching and the interchangeability of biosimilars is further complicated by the fact that HCPs may not only need to make decisions about changing from an original biological to a biosimilar, but at some point in the future may also need to consider a switch in the opposite direction, from biosimilar to original, or even from biosimilar #1 to biosimilar #2 when two or more (independently developed) biosimilars come onto the market.

Moreover, that decision may need to be reconsidered further over time as product drifts occur. It is important to realize that biosimilarity is only assured at the time of approval and there is no guarantee that biosimilarity or interchangeability is fully maintained during the lifecycle of reference and biosimilar.

Which patients, and when, to treat with biosimilars?

Switching options may be narrowed down by the limitation of which patients are appropriate targets for treatment with a biosimilar – naïve or transitioning patients. The definition of naïvety in this context is not clearly defined and interpretation may vary from country to country.

For example, the Italian Medicines Agency (AIFA) have assigned the term 'naïve' to two specific categories: (i) patients with no previous therapeutic exposure to originator ('primary naïve'), and (ii) patients with previous exposure to the originator but with a wash-out period of time adequately long based on the judgment of the clinician ('secondary naïve')[29,30]. However, there are potential variables affecting the washout period such as the drug biologic effect itself and its immunogenicity, and therefore the term 'secondary naïve' can be subject to different interpretations[29,30].

Absolute naïvety in the current context should be defined as 'no prior treatment with the reference or respective biosimilar'. However, it may be more appropriate and valuable to define those patients suitable for treatment with a biosimilar drug on a therapy-area basis, based on the volume and quality of the available post-marketing evidence.

For example, the biosimilars currently approved in oncology are used for the treatment of chemotherapy-induced anemia (biosimilar epoetins) and prevention of chemotherapy-induced neutropenia (biosimilar filgrastims). As a result of the extensive post-marketing studies conducted to address potential safety issues, patient exposure to these biosimilars is increasing[31]. As of April 2013 estimated exposure to Binocrit (a biosimilar epoetin alpha) is over 216,000 patient-years, with more than 5000 patients studied in clinical trials[31]. The current estimated exposure to Zarzio (a biosimilar filgrastim) is 3.5 million patient-days[31]. A recent review of biosimilar epoetins identified no difference in safety profiles between biosimilar and reference products, or between the alternative biosimilar formulations[32]. Similarly, a prospective, randomized controlled trial, conducted since licensing, has shown equivalence in pharmacokinetic and pharmacodynamic profiles, safety and clinical efficacy between

originator and biosimilar epoetins[33]. However this should not be interpreted as being applicable to all epoetins and all routes of applications. Indeed, for Binocrit, the subcutaneous route of administration has not been approved because of immunogenicity concerns[34].

Whilst the experience with rather small biosimilars, such as epoetins, has generally been positive, concerns have arisen about the efficacy and safety of CT-P13 (the anti-tumor necrosis factor IFX biosimilar), the extrapolation of results from rheumatologic trials to inflammatory bowel disease (IBD) and the interchangeability of CT-P13 with its reference product, Remicade[35]. The clinical biosimilarity of CT-P13 with its reference drug was established in a pharmacokinetic study of patients with ankylosing spondylitis[36] and in an efficacy study in patients with RA[37]. However, many physicians who treat patients with IBD still oppose extrapolation from other indications due to differences in mechanism of action associated with membrane-bound TNF in IBD compared with soluble TNF in the arthridites[35,38].

Extrapolation of indications for biosimilar antibodies?

The issue of extrapolation of data for indications of the originator drug which are not tested in the biosimilar is a difficult one. The assumption that no additional safety issues are expected for the extrapolated indication (based on the same mode of action) cannot always be considered automatically sufficient, particularly when the different indications involve the use of different dosages or target population[39]. For example the safety and immunogenicity may not be fully established if the study population is immune-compromised, and then extrapolated to a more immune-competent population.

Indeed translating treatment outcomes from one setting to another is not a foregone conclusion even with original biologics, as evident from the ALTTO trial in HER2-positive breast cancer[40]. Despite the promising results from an earlier trial which showed that the combined use of lapatinib and trastuzumab doubled the pathologic complete response rate compared with trastuzumab alone, there was no difference between the same two arms in a subsequent larger trial (8381 randomized patients) conducted in the adjuvant setting[40]. This clearly demonstrates that the results from trials in a specific setting/study population cannot always be extrapolated to a different study population unless corroborated by clinical trial data in that specific population.

The European Crohn's and Colitis Organisation (ECCO) position statement states that a biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication in which the reference biological has been shown to be safe and effective[41]. ECCO advocates the need for a robust trial in patients with IBD to establish its efficacy and safety for this condition. The Spanish Society of Gastroenterology task force also stated that results from studies in patients with RA should not be extrapolated to patients with IBD[42].

Conclusions

A lack of understanding amongst HCPs with the rapidly growing entry of biosimilars into the market inevitably leads to some clinical concerns. However, as the level of safety and efficacy data increases over time, so will the routine use of biosimilars across numerous therapy areas with a shift from simple biosimilar molecules in supportive care to complex biosimilar drugs for lifesaving or life-extending treatments.

The difference between biosimilarity, interchangeability and switching is still not clearly understood and is likely to become even more complex as newer biosimilar agents emerge. As yet, no guidance exists as to how this should be managed.

It is important that HCPs receive adequate education about biosimilars and that standardized terminology and nomenclature are established to enable adequate and effective introduction of biosimilars in healthcare, which are treatment options of immense clinical importance and considerable economic significance.

Transparency

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P.D. has disclosed that he is a consultant to AbbVie, Amgen and Hospira; and is on the Speakers' Bureau of AbbVie, Celltrion, Hospira, Merck Serono, and Roche. H.M. has disclosed that he is a consultant to Amgen, Hospira and Roche; and is on the Speakers' Bureau of Prime Oncology. S.D. has disclosed that he is a consultant to and is on the Speakers' Bureau of the following: Abbott Labs, AbbVie, Merck & Co., UCB Pharma, Ferring, Cellerix, Celltrion, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alfa Wasserman, Genentech, Grunenthal, Pfizer, AstraZeneca, Novo Nordisk, Cosmos Pharmaceuticals, Tigenix, Vifor and Johnson & Johnson.

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